

Albuterol multidose dry powder inhaler efficacy and safety versus placebo in children with asthma

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ABSTRACT

Background: A novel, inhalation-driven, multidose dry powder inhaler (MDPI) that does not require coordination of actuation with inhalation has been developed.

Objective: To evaluate the efficacy and safety of albuterol MDPI versus placebo MDPI after chronic dosing in children with asthma.

Methods: This phase III, double-blind, parallel-group study included children with asthma (ages, 4–11 years) with forced expiratory volume in 1 second (FEV₁) of 50–95% of predicted. After a 14-day run-in period wherein the patients continued their current asthma therapy and received single-blind placebo MDPI, they were randomized to albuterol MDPI 90 µg per inhalation, two inhalations four times daily (total daily dose, 720 µg), or placebo for 3 weeks. Pulmonary function was assessed on days 1 and 22. Efficacy and safety were evaluated by measuring the baseline-adjusted percent-predicted FEV₁ (PPFEV₁) area under the time curve over 6 hours (AUC_{0–6}) after the dose and adverse events, respectively.

Results: The full analysis set included 184 patients. Patients treated with albuterol MDPI versus patients treated with placebo MDPI had significantly greater baseline-adjusted PPFEV₁ AUC_{0–6} over 3 weeks (least squares mean difference, 25.0%•hour, which favored albuterol; $p < 0.001$). The benefit of albuterol (mean change in PPFEV₁) was evident 5 minutes after dosing and lasted several hours; the maximal effect was noted 1 to 2 hours after dosing. Albuterol MDPI was well tolerated.

Conclusions: In children with persistent asthma, albuterol MDPI improved pulmonary function significantly better than placebo MDPI over 3 weeks of treatment. Clinical efficacy was evident within 5 minutes of dosing and maintained for >2 hours. Four times daily administration was well tolerated.

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Short-acting β_2 -adrenergic agonists (e.g., albuterol) promptly reverse acute airflow obstruction and relieve bronchoconstriction and accompanying acute asthma symptoms, such as cough, chest tightness, shortness of breath, and wheezing.¹ Studies of long-term albuterol use in patients with asthma have not identified any safety concerns^{2,3}; however, there is

some evidence that long-term use of short-acting β_2 -adrenergic agonists may lead to tachyphylaxis and increased asthma exacerbations.^{4,5} Albuterol has traditionally been delivered *via* a metered-dose inhaler (MDI) in an aerosolized form or a nebulized formulation. Proper use of the MDI requires that patients coordinate device actuation with inhalation; usage errors with the MDI are common, especially among children.⁶ Incorrect inhaler technique can compromise drug delivery to the distal lung and result in poor control of asthma symptoms.⁶ Devices that use breath actuation reduce administration errors compared with conventional MDIs.⁷

A novel, inhalation-driven, multidose dry powder inhaler (MDPI) (ProAir RespiClick, Teva Pharmaceuticals, Inc., Frazer, PA) that does not require patient coordination of device actuation with inhalation was developed with the goal of reducing administration errors associated with conventional MDIs. In a recent open-label study, the use of this device was demonstrated to be well received in a study population that included patients ≥ 4 years of age and with asthma or chronic obstructive pulmonary disease: 83% of the patients reported being somewhat to very satisfied with the MDPI with an integrated dose counter, 92% were satisfied with the ease of holding and handling the

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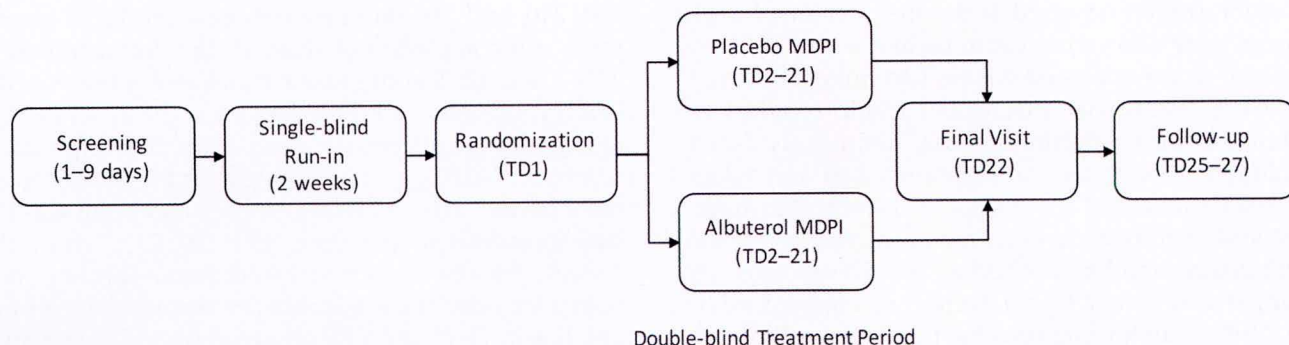


Figure 1. Study design. MDPI = Multidose dry powder inhaler; TD = treatment day.

inhaler, and 85% were satisfied with the ease of learning to use the inhaler.⁸ The safety and efficacy of albuterol MDPI in adolescents and adults have been shown to be comparable with those of an available albuterol hydrofluoroalkane (HFA) inhaler (ProAir HFA Inhalation Aerosol; Teva Respiratory LLC).

Albuterol MDPI received U.S. Food and Drug Administration approval in March 2015 for the treatment or prevention of bronchospasm in patients ages ≥ 12 years with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm in patients ages ≥ 12 years.⁹ Albuterol MDPI demonstrated safety comparable with that of a placebo MDPI in an integrated safety analysis of phase III studies of patients ages ≥ 12 years and with persistent asthma¹⁰ as well as efficacy, safety, pharmacokinetic, and pharmacodynamic profiles comparable with those of albuterol HFA in studies of adults and children ages ≥ 12 years.¹¹ A recent study demonstrated similar pharmacokinetic and pharmacodynamic profiles for albuterol MDPI and albuterol HFA in children 4–11 years of age.¹² The present study was designed to evaluate the chronic-dose efficacy and safety of albuterol MDPI relative to placebo in pediatric patients with asthma.

METHODS

Study Description and Ethics

This was an 8-week (3-week treatment exposure), randomized, double-blind, placebo-controlled, phase III trial in children (ages 4–11 years) with asthma conducted at 49 centers across the United States (www.ClinicalTrials.gov identifier: NCT02126839; ABS-AS-303) from June 10, 2014, through February 11, 2015. The study consisted of a screening period (1–9 days), a 2-week, single-blind run-in period, and a 3-week, double-blind treatment period (treatment day [TD] 1 to 22). The final treatment visit occurred on day 22, with a telephone call follow-up 3 to 5 days later (Fig. 1). Independent ethics committees or institutional review boards at each trial center approved the study protocol in accordance with local or national regulations. The trial was

conducted in full accordance with the International Council for Harmonisation Good Clinical Practice Guidelines. Parents or guardians of all enrolled patients provided written, informed consent before all study-related procedures, and assent from the patients themselves was obtained when applicable.

Patients

Patients who met the following criteria were eligible for inclusion in the study: boys or premenarchal girls ages 4 to 11 years (inclusive) with a documented diagnosis of asthma for ≥ 6 months' duration that had been stable for ≥ 4 weeks before the screening visit and on low-dose inhaled corticosteroids (≤ 200 μg fluticasone propionate per day or equivalent), leukotriene modifiers, inhaled cromones, or β_2 -agonists alone, as needed, for ≥ 4 weeks before the screening visit; forced expiratory volume in 1 second (FEV_1) 50–95% of predicted for age, height, and sex after ≥ 6 hours without β_2 -agonist use; a demonstrated prealbuterol predicted FEV_1 value of $\geq 50\%$ at all screening visits; demonstrated reversible bronchoconstriction, verified by a $\geq 15\%$ increase in FEV_1 within 30 minutes after 180 μg albuterol inhalation; and ability to self-perform peak expiratory flow (PEF) measurements with a handheld peak flow meter. The patients were required to use the MDPI device correctly, either alone or with assistance from a parent or guardian. Patients with a known sensitivity to albuterol or any of its formulation excipients, a history of respiratory tract infection or disorder that was not resolved within 4 weeks before the screening visit, an asthma exacerbation that required oral corticosteroids within 3 months or hospitalization within 6 months of the screening visit, or a history of life-threatening asthma were ineligible to participate. Also excluded were patients who used prohibited concomitant medications, were treated with oral or injectable corticosteroids within 6 weeks of the screening visit, or participated in a previous albuterol MDPI trial at any time or received any investigational drug as part of a trial within 30 days of the screening visit.

Randomization occurred at the first treatment visit. Patients were allowed to continue in the study if they remained in general good health, had not experienced an adverse event (AE) that would result in failure to continue to meet selection criteria, had not used any prohibited concomitant medications, had not taken any rescue albuterol for ≥ 6 hours before each treatment visit, continued to demonstrate correct use of the MDPI device, and had not had an asthma exacerbation or upper respiratory tract infection or received additional treatment for asthma other than rescue albuterol. Patients' average predose FEV₁ values at treatment visits could not exceed $\pm 20\%$ of the screening visit value, and each predose interval was to remain 50–95% of the predicted value.

Study Design

After an initial screening visit (1–9 days), eligible patients entered the single-blind 2-week run-in period, during which they continued to use their current asthma therapy and received single-blind placebo MDPI and an albuterol HFA MDI (ProAir HFA; Teva) to use as needed for the relief of acute asthma symptoms. At treatment visit 1, the patients were randomized (1:1 ratio) to receive albuterol MDPI 90 μg per inhalation or placebo MDPI as two inhalations (180 μg /dose) four times daily (~ 7 A.M., 12 noon, 5 P.M., and bedtime; a total daily dose of 720 μg) for 3 weeks. The patients maintained their current asthma therapy throughout the study; however, dosing with these concurrent medications was withheld the morning of each treatment-evaluation visit and was delayed until the end of the study visit. The assigned treatments were defined by a randomization code number assigned through an interactive voice response system/interactive Web response system. Only one randomization list was generated. Eligible patients were assigned the next available randomization number according to a centrally generated randomization list. The patients and investigators remained blinded to the randomized treatment assignments during the study. The sponsor's clinical personnel also were blinded to study drug identity after the single-blind, run-in period until the data base was locked for analysis and the treatment assignments were revealed.

Assessment of Efficacy

Determinations of FEV₁ values were made by using standardized spirometers. Predicted FEV₁ values were computed and adjusted for age, height, and sex for patients ages 4–5 years¹³ and for patients ages 6–11 years¹⁴ by using American Thoracic Society/European Respiratory Society criteria applicable to pediatric patients.¹⁵ Serial FEV₁ measurements (the highest of three acceptable maneuvers) were obtained 5, 15, 30, 45, 60,

120, 240, and 360 minutes after baseline FEV₁ assessment and completion of study drug administration at TDs 1 and 22. The primary efficacy end point was the baseline-adjusted percent-predicted FEV₁ (PPFEV₁) area under the effect-time curve from time 0 (predose) to 6 hours (AUC_{0–6}) after dosing over the 3-week treatment period. The secondary efficacy end point was the baseline-adjusted postdose PEF AUC_{0–6} over the 3-week treatment period. Additional efficacy end points included the maximum percentage change from baseline in FEV₁ and PEF observed up to 2 hours after completion of dosing over the 3-week treatment period and at TDs 1 and 22; baseline-adjusted PPFEV₁ AUC_{0–6} and PEF AUC_{0–6} at TDs 1 and 22; time to maximum FEV₁ and PEF at TDs 1 and 22; time, in minutes, to a $\geq 15\%$ and a $\geq 12\%$ increase in baseline FEV₁ and PEF in patients who met this increase within 30 minutes after dosing on TDs 1 and 22; duration, in hours, of an increase of $\geq 15\%$ or $\geq 12\%$ above baseline within 6 hours after dosing in patients who responded within 30 minutes on TDs 1 and 22; and the absolute and relative numbers of patients with a 12% and 15% increase in baseline FEV₁ and PEF within 30 minutes after dosing on TDs 1 and 22.

The patients received a paper diary during the run-in and treatment periods, and were required to make daily entries throughout the study. Compliance with diary entries was assessed during the run-in period. Daily diary end points included changes from baseline in the percentage of symptom-free days, rescue medication-free 24-hour periods, and evenings without asthma-related awakenings. Other diary variables included changes in daily (A.M.) predose PEF and in the number of asthma-related nocturnal awakenings per week, puffs of rescue medication per 24-hour period, and puffs of rescue medication per evening. Asthma symptoms, including wheezing, shortness of breath, cough, and chest tightness, were recorded at the end of each day. The six-point Asthma Symptom Score (0, no symptoms during the day; 5, symptoms severe enough to interfere with normal daily activities) was recorded daily. Changes from baseline to TD 21 were evaluated.

Assessment of Safety and Tolerability

AEs were monitored throughout the trial and were defined as any untoward medical occurrence (e.g., physical sign, symptom, or laboratory parameter) or medical condition that developed or worsened in severity, regardless of its relationship to the study drug. Serious AEs included death, a life-threatening event, hospitalization or prolongation of hospitalization, persistent or significant disability, congenital anomaly or birth defect, or any event that jeopardized the patient and required medical intervention to prevent one of the aforementioned outcomes. Physical examinations,

vital signs, and electrocardiograms were conducted on TDs 1 and 22. An asthma exacerbation was defined as any worsening of asthma that required treatment other than rescue albuterol and/or regular inhaled corticosteroid use, including the use of systemic corticosteroids and/or an emergency department visit or hospitalization that resulted in a change in the patient's regular inhaled corticosteroid dose or the addition of other asthma medications. An exacerbation was not considered an AE unless it met the criteria for a serious AE. A patient who experienced an exacerbation was not discontinued from the trial unless the event met serious AE criteria or the investigator believed that it was in the patient's best interest to withdraw from the study.

Statistical Analyses

By using data from previous, similarly designed studies in children with asthma, it was determined that a sample size of 80 patients per treatment group would have 90% power to detect a difference of $\geq 11.0\% \cdot \text{hour}$ (residual standard deviation, $23.7\% \cdot \text{hour}$) at both TD 1 and TD 22 in baseline-adjusted PPFEV₁ AUC₀₋₆. When assuming a 10% dropout rate, this number was increased to 90 patients per treatment group. All efficacy analyses were performed on the full analysis set, defined as all randomized patients who received one or more doses of the study drug and had one or more postbaseline assessments. All safety assessments were performed on the safety population, which included all randomized patients who took one or more doses of the study drug. Patient demographic data were summarized descriptively. A mixed-model, repeated-measures analysis was used to evaluate efficacy end points derived from spirometry measurements on study days 1 and 22. Treatment group, study day, and their interaction were analyzed as fixed effects with the visit-specific baseline value as a covariate. An unstructured covariance matrix between repeated measures was assumed. Treatment-group least squares (LS) means and their corresponding 95% confidence intervals were used to calculate between-group differences. A similar model was used to evaluate weekly averages of daily diary data at each study week. Percentage changes from baseline in selected diary measures over the treatment period were analyzed with an analysis of covariance model with the baseline weekly average as the covariate. There was a single primary and secondary variable; additional analyses were not adjusted for multiplicity.

RESULTS

Patient Disposition and Baseline Characteristics

A total of 377 patients were screened at 49 centers in the United States, and 211 patients were enrolled in the

study. Of the 166 patients who were screened but not enrolled, 136 did not meet inclusion criteria. Of these 136 patients, 77 (56.6%) did not meet reversibility criteria and 22 (16.2%) were unable to perform reproducible spirometry. Twenty-five patients were enrolled but not randomized for various reasons (Fig. 2). A total of 186 patients were randomized (intent-to-treat population): 92 to the placebo MDPI group and 94 to the albuterol MDPI group. The safety population consisted of 185 patients; the full analysis set consisted of 184 patients. Ten and 14 patients withdrew from the study in the placebo MDPI and albuterol MDPI groups, respectively (Fig. 2). In general, baseline demographics and clinical characteristics were similar between the treatment groups. The most common comorbidities were allergic rhinitis, eczema, and seasonal allergies. Nearly every patient had taken previous medications for obstructive airway disease, more than half had taken systemic antihistamines, and nearly a fourth had taken nasal preparations (Table 1).

Efficacy

Over the 3-week treatment period, the patients who were treated with albuterol MDPI experienced significant improvements in pulmonary function; the LS mean difference in baseline-adjusted PPFEV₁ AUC₀₋₆ (primary efficacy variable) was $25.0\% \cdot \text{hour}$ in favor of albuterol MDPI versus placebo MDPI (95% confidence interval, 16.1–33.9; $p < 0.001$). Results by treatment group are summarized in Table 2. On TDs 1 and 22, the patients who received albuterol MDPI had significantly greater baseline-adjusted PPFEV₁ AUC₀₋₆ compared with patients who received placebo MDPI ($p < 0.001$) (Table 3). Likewise, over 3 weeks of treatment, the patients who were treated with albuterol MDPI experienced a significant improvement in baseline-adjusted PEF AUC₀₋₆ compared with those who received placebo MDPI; the LS mean difference was $76.3 \text{ L/min} \cdot \text{hour}$ in favor of albuterol MDPI versus placebo MDPI (95% confidence interval, 47.8–104.9; $p < 0.001$). Results by treatment group and by TD are summarized in Tables 2 and 3, respectively. Similarly, improvements in baseline-adjusted PEF AUC₀₋₆ on TDs 1 and 22 also favored albuterol MDPI versus placebo MDPI (Table 3). Overall, for FEV₁ and PEF, the median durations of the 12% and 15% response rates on TDs 1 and 22 ranged from ~1 to 4 hours (Table 4).

The maximum percentage change from baseline in FEV₁ and PEF within 2 hours of dosing was significantly greater in patients treated with albuterol MDPI compared with those who received placebo over the 3-week treatment period, on TD 1, and on TD 22 ($p < 0.001$) (Tables 2 and 3). The numbers and percentages of patients who responded with a 12% or a 15% increase in FEV₁ or PEF from baseline within 30 minutes

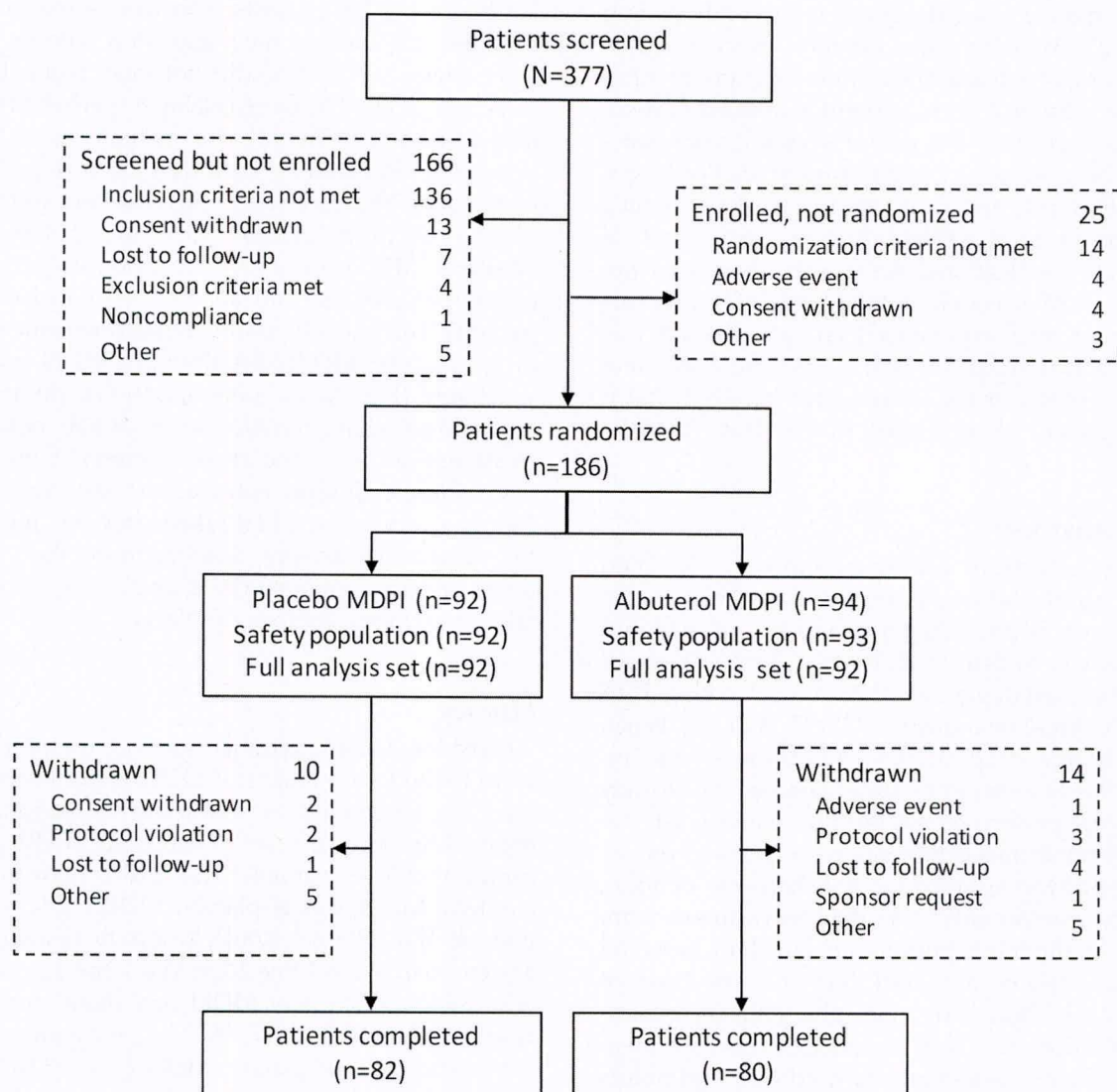


Figure 2. Patient flow. MDPI = Multidose dry powder inhaler.

after dosing were significantly ($p < 0.001$) higher in the albuterol MDPI group compared with the placebo group for all measures (Table 3). The time to the onset and duration of the 12% and the 15% response levels are summarized in Table 4. On TD 1, the median times to 12% and 15% response onsets in FEV₁ were just under 6 minutes. On TD 22, the median time to 12% response onset in FEV₁ was shorter than that for the 15% response onset. On TD 1, median times to the 12% and the 15% response onset in PEF were just >5 minutes, and, on TD 22, the median time to 12% response onset was shorter than that for the 15% response onset.

The results from the daily diaries are summarized in Table 5. Overall, there were no significant between-treatment-group differences in changes from baseline to TD 21 in the percentage of symptom-free days, rescue medication-free 24-hour periods, or nights without asthma-related awakenings; however, numer-

ical differences favored patients treated with albuterol. Likewise, there were no significant between-treatment-group differences in LS mean change from baseline to TD 21 for the daytime Asthma Symptom Score, asthma-related nocturnal awakenings per week, morning predose PEF, puffs of rescue medication per 24 hours, and puffs of rescue medication per evening.

Safety and Tolerability

During the 3-week treatment period, 23% of the patients in each treatment group experienced AEs, with a low overall incidence ($\leq 4\%$). The most frequently occurring AE in both treatment groups was headache. In the placebo MDPI group, other commonly reported AEs included pyrexia, upper abdominal pain, cough, upper respiratory tract infection, and ligament sprain. In the albuterol MDPI group, cough and vomiting

Table 1 Baseline demographic and clinical characteristics of randomized patients

Characteristic	Placebo MDPI Group (n = 92)	Albuterol MDPI Group (n = 94)
Age, mean $\pm$ SD (range), y	8.5 $\pm$ 1.8 (4–11)	8.3 $\pm$ 1.7 (4–11)
Age group, no. (%)		
4–7 y	23 (25.0)	30 (31.9)
8–11 y	69 (75.0)	64 (68.1)
Boys, no. (%)	55 (59.8)	52 (55.3)
Race, no. (%)		
White	41 (44.6)	40 (42.6)
Black	48 (52.2)	52 (55.3)
Other	3 (3.3)	2 (2.1)
Ethnicity, Hispanic/Latino, no. (%)	11 (12.0)	14 (14.9)
Body mass index, mean $\pm$ SD, kg/m ²	19.5 $\pm$ 5.0	19.4 $\pm$ 5.3
FEV ₁ , mean $\pm$ SD, L	1.7 $\pm$ 0.4	1.6 $\pm$ 0.4
PPFEV ₁ , mean $\pm$ SD, %	87.5 $\pm$ 11.5	89.0 $\pm$ 12.4
Airway reversibility, mean $\pm$ SD, %	22.0 $\pm$ 8.1	22.9 $\pm$ 8.2
Comorbid conditions of $\geq 10\%$, no. (%)		
Allergic rhinitis	52 (56.5)	41 (43.6)
Eczema	22 (23.9)	31 (33.0)
Seasonal allergy	24 (26.1)	28 (29.8)
Perennial rhinitis	17 (18.5)	23 (24.5)
Food allergy	16 (17.4)	14 (14.9)
Attention deficit hyperactivity disorder	17 (18.5)	9 (9.6)
Headache	13 (14.1)	7 (7.4)
Previous medications of $\geq 20\%$, no. (%)		
Drugs for obstructive airway disease	92 (100)	93 (98.9)
Systemic antihistamines	53 (57.6)	59 (62.8)
Nasal preparations	22 (23.9)	22 (23.4)

MDPI = Multidose dry powder inhaler; SD = standard deviation; FEV₁ = forced expiratory volume in 1 s; PPFEV₁ = percent-predicted forced expiratory volume in 1 s.

Table 2 Results for the primary and additional key efficacy end points during the 3-week treatment period, full analysis set

Variable (LS mean)	Placebo MDPI Group (n = 92)	Albuterol MDPI Group (n = 92)	p
Baseline-adjusted PPFEV ₁ AUC _{0–6} , %•hr	18.71	43.73	<0.001
Maximum percentage change from baseline in FEV ₁ observed ≤ 2 hr after completion of dosing	10.39	20.00	<0.001
Baseline-adjusted PEF AUC _{0–6} , L/min•hr	71.52	147.85	<0.001
Maximum percentage change from baseline in PEF observed ≤ 2 hr after completion of dosing	13.84	25.57	<0.001

LS = Least squares; MDPI = multidose dry powder inhaler; PPFEV₁ = percent-predicted forced expiratory volume in 1 s; AUC_{0–6} = area under the effect-time curve from time 0 (predose) to 6 hr (postdose); FEV₁ = forced expiratory volume in 1 s; PEF = peak expiratory flow (rate).

were commonly reported (Table 6). There were no deaths, serious AEs, or withdrawals due to AEs, and none of the reported AEs was deemed to be related to the study drug. Four patients in the placebo MDPI group and five patients in the albuterol MDPI group

experienced an asthma exacerbation; all nine cases were moderate in severity. Eight patients recovered or were recovering, and one patient on placebo MDPI had not recovered. No patient with an asthma exacerbation was discontinued from the study; however, five pa-

Table 3 Results for additional efficacy end points by treatment day, full analysis set

Variable	Treatment Day 1			Treatment Day 22		
	Placebo MDPI Group (n = 92)*	Albuterol MDPI Group (n = 92)*	p Value#	Placebo MDPI Group (n = 82)*	Albuterol MDPI Group (n = 80)*	p Value#
Volume measures						
Baseline-adjusted PPFEV ₁ AUC ₀₋₆ , %•hr	19.08	45.32	<0.001	18.34	42.14	<0.001
Maximum percentage change from baseline in FEV ₁ observed ≤2 hr after dosing	10.59	20.13	<0.001	10.20	19.86	<0.001
Patients with a 12% increase in FEV ₁ within 30 min, no. (%)	21 (22.8)	63 (68.5)	<0.001	15 (18.3)	52 (65.0)	<0.001
Patients with a 15% increase in FEV ₁ within 30 min, no. (%)	16 (17.4)	48 (52.2)	<0.001	10 (12.2)	42 (52.5)	<0.001
Rate measures						
Baseline-adjusted PEF AUC ₀₋₆ , L/min•hr	80.14	165.24	<0.001	62.89	130.46	0.001
Maximum percentage change from baseline in PEF (L/min) observed ≤2 hr after dosing	15.34	28.01	<0.001	12.35	23.12	<0.001
Patients with a 12% increase in PEF within 30 min, no. (%)	31 (33.7)	77 (83.7)	<0.001	22 (26.8)	57 (71.3)	<0.001
Patients with a 15% increase in PEF within 30 min, no. (%)	27 (29.3)	63 (68.5)	<0.001	13 (15.9)	50 (62.5)	<0.001

MDPI = Multidose dry powder inhaler; PPFEV₁ = percent-predicted forced expiratory volume in 1 s; AUC₀₋₆ = area under the effect-time curve from time 0 (predose) to 6 hours (postdose); FEV₁ = forced expiratory volume in 1 s; PEF = peak expiratory flow (rate).

*Denotes the number of patients with data at each visit.

#Based on the least squares means.

Data are least squares means unless otherwise indicated.

Table 4 Summary statistics for response onset and duration after albuterol MDPI by treatment day, full analysis set

	Treatment Day 1		Treatment Day 22	
	FEV ₁	PEF	FEV ₁	PEF
Time to 12% response onset				
No. patients*	63	77	52	57
Mean $\pm$ SD, min	11.5 $\pm$ 9.8	10.3 $\pm$ 9.2	11.1 $\pm$ 8.5	10.6 $\pm$ 8.5
Median, min	5.8	5.4	5.7	5.7
Range, min	3.1–32.0	3.1–33.1	3.4–31.8	3.4–31.0
Duration of 12% response				
No. patients*	63	77	52	57
Mean $\pm$ SD, hr	2.8 $\pm$ 2.3	3.6 $\pm$ 2.4	2.8 $\pm$ 2.2	2.6 $\pm$ 2.4
Median, hr	2.0	4.0	2.1	1.0
Range, hr	0.2–6.0	0.2–6.1	0.2–6.1	0.2–6.0
Time to 15% response onset				
No. patients*	48	63	42	50
Mean $\pm$ SD, min	12.3 $\pm$ 9.9	9.5 $\pm$ 7.9	13.2 $\pm$ 9.7	13.6 $\pm$ 9.8
Median, min	5.9	5.4	8.9	10.6
Range, min	3.1–31.7	3.1–30.3	3.4–31.8	3.4–31.2
Duration of 15% response				
No. patients*	48	63	42	50
Mean $\pm$ SD, hr	2.4 $\pm$ 2.3	3.6 $\pm$ 2.4	2.8 $\pm$ 2.2	2.8 $\pm$ 2.3
Median, hr	0.9	4.0	2.0	2.0
Range, hr	0.2–6.0	0.2–6.0	0.2–6.1	0.2–6.0

MDPI = Multidose dry powder inhaler; FEV₁ = forced expiratory volume in 1 s; PEF = peak expiratory flow (rate); SD = standard deviation.

*The number of patients with data at each visit.

Table 5 Results for daily diary variables, full analysis set

Variable	Placebo MDPI Group (n = 92)	Albuterol MDPI Group (n = 92)	p Value
Change from baseline to TD 21 in percentage of the following:			
Symptom-free days	−1.38	3.85	0.07
Rescue medication-free 24-hr periods	−2.44	1.69	0.14
Nights without asthma-related awakenings	2.77	0.41	0.22
LS mean change from baseline to TD 21 in the following:			
Daily (daytime) asthma symptom score	0.00	−0.09	0.25
Asthma-related nocturnal awakenings/wk	−0.31	0.05	0.22
Daily A.M. predose PEF, L/min	4.84	9.55	0.17
Puffs of rescue medication per 24-hr periods	−0.05	−0.06	0.93
Puffs of rescue medication per evening	−0.02	−0.03	0.91

MDPI = Multidose dry powder inhaler; TD = treatment day; LS = least squares; PEF = peak expiratory flow (rate).

tients were discontinued because they received a prohibited medication (*i.e.*, systemic corticosteroids).

DISCUSSION

This randomized trial conducted in children with asthma, ages 4–11 years, demonstrated that 3 weeks of

treatment with two inhalations of albuterol MDPI 90 μ g four times daily (a total daily dose of 720 μ g) was effective for improving pulmonary function and was generally well tolerated. After 3 weeks of treatment, the patients who received albuterol MDPI had significantly greater baseline-adjusted PPFEV₁ AUC_{0–6} (pri-

Table 6 Summary of treatment-emergent adverse events occurring in at least 2% of patients in any treatment group, safety population

Adverse Event*	Placebo MDPI Group (n = 92)	Albuterol MDPI Group (n = 93)
Headache	4 (4.3)	3 (3.2)
Cough	3 (3.3)	3 (3.2)
Pyrexia	3 (3.3)	2 (2.2)
Abdominal pain, upper	3 (3.3)	0 (0.0)
URTI	3 (3.3)	0 (0.0)
Ligament sprain	3 (3.3)	0 (0.0)
Seasonal allergy	2 (2.2)	0 (0.0)
Vomiting	1 (1.1)	3 (3.2)
Nasopharyngitis	1 (1.1)	2 (2.2)
Oropharyngeal pain	1 (1.1)	2 (2.2)

MDPI = Multidose dry powder inhaler; URTI = upper respiratory tract infection.

*Medical Dictionary for Regulatory Activities preferred terms.

mary end point) and PEF AUC₀₋₆ (secondary end point) compared with those who received placebo. In addition, albuterol MDPI was numerically superior to placebo MDPI for most of the other efficacy end points, including baseline-adjusted PPFEV₁ AUC₀₋₆ and PEF AUC₀₋₆ on TDs 1 and 22, and maximum percentage change from baseline in FEV₁ and PEF. However, the *p* values for these variables were not adjusted for multiplicity. In a recent study conducted in children 4–11 years of age, albuterol MDPI and albuterol HFA provided similar improvements in pulmonary function compared with placebo when administered as a single 90- or 180- μ g dose.¹⁶

More patients treated with albuterol MDPI (52.2%) than patients who received placebo MDPI (17.4%) responded to therapy, as assessed by the percentage of patients who achieved a 15% increase in FEV₁ from baseline within 30 minutes after dosing. The median time to achieve this response was rapid, with a median time to onset of ~6 to 9 minutes for an increase of 15% in FEV₁ from baseline within 30 minutes of dosing.

The improvements from baseline in FEV₁ noted in the patients treated with albuterol MDPI were similar on day 1 and on day 22, which indicated that there was no tachyphylaxis as a result of chronic albuterol use over the 3-week study period. The improvements noted on day 1 indicated the effectiveness of albuterol MDPI as a rescue inhaler on an as-needed basis for quick relief, whereas the continued effectiveness noted on day 22 indicated that patients would continue to experience benefit even after repeated use. Although

previous results indicate that chronic use of β agonists in asthma may result in more exacerbations, the present study did not observe an increase as a result of albuterol MDPI treatment in comparison with placebo.¹⁷ In the present study, nearly 100% of patients were previously taking medication for obstructive airway disease. It may be a possibility that these concomitant medications provided some level of protection from tachyphylaxis.

The four times daily administration of albuterol MDPI and placebo MDPI over a 3-week treatment period was well tolerated among pediatric patients, with comparable tolerability profiles between the treatment groups. Notably, four times daily dosing is not the recommended dosing schedule; more typically, as-needed dosing is used in clinical practice. Therefore, any AEs or attenuation of effect would likely be much less with the less frequent dosing used in the real-world setting. The overall incidence of treatment-emergent AEs was $\leq 4\%$. There were no serious AEs, and none of the events was considered to be treatment related. Nine patients experienced asthma exacerbations; eight of the nine cases recovered or were recovering. These findings were generally consistent with the known tolerability profile of albuterol and other short-acting β_2 -adrenergic agonists and consistent with two previously conducted studies in adults on the tolerability of albuterol MDPI administered four times daily for a total daily dose of 720 μ g over a 12-week period.¹⁰

CONCLUSION

Albuterol MDPI, administered four times daily for 3 weeks, improved pulmonary function in pediatric patients significantly better than placebo. Clinical effects were evident within 5 minutes after dosing and were maintained for >2 hours, with no evidence for diminution of the effect with chronic use. The four times daily administration was generally well tolerated in pediatric patients. The U.S. Food and Drug Administration reviewed the data from this clinical trial in its evaluation, and the April 2016 approval of the albuterol MDPI expanded the indication for treatment of patients ≥ 4 years of age.

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